DETAILED ACTION

Currently claims 1-12 and 14-18 are pending in the application.

Election/Restrictions

Restriction is required under 35 U.S.C. 121 and 372.

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

In accordance with 37 CFR 1.499, applicant is required, in reply to this action, to elect a single invention to which the claims must be restricted.

Group I, claim(s) 1-11 and 15-18 (in part), drawn to compounds of formula (I) and compositions thereof where the A is a 1,2-diazole ring. If Group I is elected, further election of a species is required.

Group II, claim(s) 1-11 and 15-18 (in part), drawn to compounds of formula (I) and compositions thereof not covered in Group I. If Group II is elected, further election of a species is required. Also, further restriction will limit the scope of Group II to single heterocycle for ring A.

Group III, claim(s) 12, drawn to a method of use of the compounds of claim 1. If Group III is elected, further election of a species is required. Also, further restriction will the limit to the scope of Group III to one of the compounds Groups listed as I-II.

Group IV, claim(s) 14, drawn to a method of preparing compounds of formula (I). If Group IV is elected, further election of a species is required. Also, further restriction will the limit to the scope of Group IV to one of the compounds Groups listed as I-II.

The inventions listed as Groups I-IV do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: Groups I-IV lack unity of invention because even though the inventions of these groups require the technical feature of a biaryl compound containing a fused heterocycle on one of the aryl groups, this technical feature is not a special technical feature as it does not make a contribution over the prior art in view of U.S. Patent Application No. US 2004/0138287 A1 by Barth et al. (NOTE: This reference was provided in the international search report filed 28 July 2006) Barth et al. report compounds containing an indole ring bound directly an group. See, for example, the compounds of Table 1 on page 8.

Election of Species

This application contains claims directed to more than one species of the generic invention. These species are deemed to lack unity of invention because they are not so linked as to form a single general inventive concept under PCT Rule 13.1.

The following compounds are representative of the species claimed:

The compound of claim 1 where ring A is substituted by a morpholine ring, the compound of claim 1 where ring A is substituted by a piperazine ring, and the compound of claim 1 where ring A is substituted by a piperidine ring.

Applicant is required, in reply to this action, to elect a single species to which the claims shall be restricted if no generic claim is finally held to be allowable. The reply must also identify the claims readable on the elected species, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered non-responsive unless accompanied by an election.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 CFR 1.141. If claims are added after the election, applicant must indicate which are readable upon the elected species. MPEP § 809.02(a).

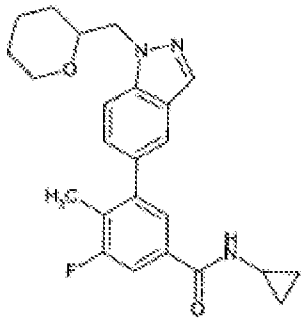
The following claim(s) are generic: Claim 1.

The species listed above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, the species lack the same or corresponding special technical features for the following reasons: even though the inventions of these groups require the technical feature of a biaryl compound containing a fused heterocycle on one of the aryl groups, this technical feature is not a special technical feature as it does not make a contribution over the prior art in view of U.S. Patent Application No. US

2004/0138287 A1 by Barth et al. (NOTE: This reference was provided in the international search report filed 28 July 2006).

During a telephone conversation with Dara Dinner on 9 April 2009 a provisional election was made of the compound of Example 1 on page 41 of the specification (depicted below) with traverse to prosecute the invention of Group I, claims 1-11 and 15-18 (in part). Affirmation of this election must be made by applicant in replying to this Office action.

Example 1



Claims 12 and 14 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected inventions, there being no allowable generic or linking claim.

As per MPEP 803.02, the examiner will determine whether the entire scope of the claims is patentable. Applicants' elected species is not allowable. Therefore, according to MPEP 803.02:

> Following election, the Markush-type claim will be examined fully with respect to the elected species and further to the extent necessary to determine patentability. If the Markush-type claim is not allowable, the provisional election will be given effect and examination will be limited to the Markush-type claim and claims to the elected species, with claims drawn to species patentably distinct from the elected species held withdrawn from further consideration.
>
> If on examination the elected species is found to be anticipated or rendered obvious by prior art, the Markush-type claim and claims to the elected species shall be rejected, and claims to the nonelected species would be held withdrawn from further consideration. As the elected species has been found not allowable, the Markush-type claims have been

rejected and claims to the nonelected invention held withdrawn from further consideration.

Claims 1-11 and 15-18 **have been examined to the extent that they are readable on the elected embodiment, the elected species of** the compound of Example 1. Since the elected species is not allowable, subject matter not embraced by the elected embodiment is therefore withdrawn from further consideration. It has been determined that the entire scope claimed is not patentable.

Priority

This application is a 35 U.S.C. 371 National Stage Filing of International Application No. PCT/GB05/00281, filed 27 January 2005, which claims priority under 35 U.S.C. 119(a-d) to United Kingdom Application 0402140.8, filed 30 January 2004.

Information Disclosure Statement

The Examiner has considered the Information Disclosure Statements filed on 18 December 2008 and 28 July 2006.

Claim Objections

Claims 12 and 14 are objected as being drawn to non-elected subject matter.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

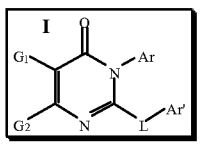
> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-11 and 15-18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compounds of formula (I), a pharmaceutically acceptable salt of a compound of formula (I) as well as carbamates and amide derivatives of compounds of formula (I), does not reasonably provide enablement for pharmaceutically acceptable derivatives (as defined in the specification, page 7) that are not pharmaceutically acceptable salts, carbamates or amides of a compound of formula (I). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is *undue*. These factors include, but are not limited to: (a) breadth of the claims; (b) nature of the invention; (c) state of the prior art; (d) level of one of ordinary skill in the art; (e) level of predictability in the art; (f) amount of direction provided by the inventor; (g) existence of working examples; and (h) quantity of experimentation needed to make or use the invention based on the content of the disclosure. (See *Ex parte Forman* 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988).

The above factors, regarding the present invention, are summarized as follows:

(a) *Breadth of the claims* - the breadth of the claims includes the compounds of formula (I) as well as pharmaceutically acceptable derivatives thereof;



(b) *Nature of the invention* - the nature of the invention is drawn to compounds of formula (I) for use in the treatment of a condition or disease state mediated by p38 kinase;

(c) *State of the prior art - Nature Reviews: Drug Discovery* offers a snapshot of the state of the drug development art. Herein, drug development is stated to follow the widely accepted Ehrlich model which includes: 1) development of a broad synthetic organic chemistry program; 2) subsequent testing of compounds in an appropriate laboratory model for the disease to be treated; and 3) screening of compounds with low toxicity in prospective clinical trials (Jordan, V. C. *Nature Reviews: Drug Discovery,* 2, **2003**, p. 205);

(d) *Level of one of ordinary skill in the art* - the artisans synthesizing applicant's pharmaceutically acceptable derivatives of the compounds of formula (I), would be a collaborative team of synthetic chemists and/or health practitioners, possessing commensurate degree level and/or skill in the art, as well as several years of professional experience;

(e) *Level of predictability in the art* - Synthetic organic chemistry is quite unpredictable (*In re Marzocchi and Horton* 169 USPQ at 367 ¶ 3). The following excerpt is taken from Dörwald, which has extreme relevance to the synthesis of *oxidative metabolite(s)* the compounds of formula (I) (Dörwald, F. Zaragoza. *Side Reactions in Organic Synthesis: A Guide to Successful Synthesis Design*, Weinheim: WILEY-VCH Verlag GmbH & Co. KGaA, **2005**, Preface):

> *Most non-chemists would probably be horrified if they were to learn how many attempted syntheses fail, and how inefficient research chemists are. The ratio of successful to unsuccessful chemical experiments in a normal research laboratory is far below unity, and synthetic research chemists, in the same way as most scientists, spend most of their time working out what went wrong, and why.*
>
> *Despite the many pitfalls lurking in organic synthesis, most organic chemistry textbooks and research articles do give the impression that organic reactions just proceed smoothly and that the total synthesis of complex natural products, for instance, is maybe a labor-intensive but otherwise undemanding task. In fact, most syntheses of structurally complex natural products are the result of several years of hard work by a team of chemists, with almost every step requiring careful optimization. The final synthesis usually looks quite different from that originally planned, because of unexpected difficulties encountered in the initially chosen synthetic sequence. Only the seasoned practitioner who has experienced for himself the many failures and frustrations which the development (sometimes even the repetition) of a synthesis usually implies will be able to appraise such work.*
>
> *Chemists tend not to publish negative results, because these are, as opposed to positive results, never definite (and far too copious).*

Similarly, the following excerpt is taken from Vippagunta, et al. with respect to the synthesis of *solvates* and *hydrates* of formula I (Vippagunta, et al. *Advanced Drug Delivery Reviews*, 48, **2001**, p. 18):

Predicting the formation of solvates or hydrates of a compound and the number of molecules of water or solvent incorporated into the crystal lattice of a compound is complex and difficult. Each solid compound responds uniquely to the possible formation of solvates or hydrates and hence generalizations cannot be made for a series of related compounds. Certain molecular shapes and features favor the formation of crystals without solvent; these compounds tend to be stabilized by efficient packing of molecules in the crystal lattice, whereas other crystal forms are more stable in the presence of water and/or solvents. There may be too many possibilities so that no computer programs are currently available for predicting the crystal structures of hydrates and solvates.

Finally, the following excerpt is taken from Burger's with respect to the synthesis of *prodrugs* of the compounds of formula (I) or salts thereof (Wolff, Manfred E., Ed. *Burger's Medicinal Chemistry and Drug Discovery - Fifth Edition,* New York: John Wiley & Sons, **1996**, vol. 1, pp. 975-976):

The design of prodrugs in a rational manner requires that the underlying causes which necessitate or stimulate the use of the prodrug approach be defined and clearly understood. It may then be possible to identify the means by which the difficulties can be overcome. The rational design of the prodrug can thus be divided into three basic steps: (1) identification of the drug delivery problem; (2) identification of the physiochemical properties required for optimal delivery; and (3) selection of a prodrug derivative that has the proper physiochemical properties and that will be cleaved in the desired biological compartment.

The difficulty of extrapolating data from animal to humans encountered during toxicokinetic and toxicologic studies with drugs is amplified with prodrugs, since not only metabolism of the active moiety might differ, but also its availability from the prodrug. As a matter of fact, there is presently no published rational for the conduct of animal and human pharmacokinetic programs during prodrug research and development.

(f) *Amount of direction provided by the inventor* - The application is negligent regarding direction with respect to making derivatives of the compounds of formula (I) with the exceptions that Applicant has demonstrated the synthesis of carbamates and amides of compounds of formula (I). These demonstrated derivatives do not, however, provide reasonable direction for the vast array of compounds encompassed by the generic terms "prodrug" or "derivatives."

(g) *Existence of working examples* - applicant has provided sufficient guidance to make and use the compounds of formula (I), a pharmaceutically acceptable salt of a compound of formula (I) as well as carbamates and amides derivatives of compounds of formula

(I); however, the specification lacks working examples of pharmaceutically acceptable derivatives (as defined in the specification, page 7) that are not pharmaceutically acceptable salts, carbamates or amides of a compound of formula (I).

Within the specification, "specific operative embodiments or examples of the invention must be set forth. Examples and description should be of sufficient scope as to justify the scope of the claims. *Markush* claims must be provided with support in the disclosure for each member of the *Markush* group. Where the constitution and formula of a chemical compound is stated only as a probability or speculation, the disclosure is not sufficient to support claims identifying the compound by such composition or formula." See MPEP § 608.01(p).

(h) *Quantity of experimentation needed to make or use the invention based on the content of the disclosure* - predicting whether a recited compound is in fact one that produces a desired physiological effect at a therapeutic concentration and with useful kinetics, is filled with experimental uncertainty, and without proper guidance, would involve a substantial amount of experimentation (Jordan, V. C. *Nature Reviews: Drug Discovery*, 2, **2003**, pp. 205-213).

A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. {*In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)}.

The determination that *undue experimentation* would have been needed to make and use the claimed invention is not a single, simple factual determination. Rather, it is a conclusion reached by weighing all the above noted factual considerations. (*In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404). These factual considerations are discussed comprehensively in MPEP § 2164.08 (scope or breadth of the claims), § 2164.05(a) (nature of the invention and state of the prior art), § 2164.05(b) (level of one of ordinary skill), § 2164.03 (level of predictability in the art and amount of direction provided by the inventor), § 2164.02 (the existence of working examples) and § 2164.06 (quantity of experimentation needed to make or use the invention

based on the content of the disclosure).

Based on a preponderance of the evidence presented herein, the conclusion that applicant is insufficiently enabled for pharmaceutically acceptable derivatives (as defined in the specification, page 7) that are not pharmaceutically acceptable salts, carbamates or amides of a compound of formula (I) is clearly justified.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 7 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Regarding claim 7, the phrase "substantially as hereinbefore defined with reference to any one of Examples 1 to 9" renders the claim indefinite because it is unclear how the structures of the claimed compounds relate to those of Examples 1 to 9. It is suggested that the claim be amended to define the structural variance of the claimed compounds.

Claim 7 is further rejected because it refers to Examples 1 to 9 of the instant specification. A claim should particularly point out and distinctly claim the subject matter which the applicant regards as his invention, and should stand alone to define the invention. Incorporation into claims by express reference to specification in this situation is not permitted, because one must refer back to the specification to determine what applicant is claiming by referring to the examples. It is suggested that applicant insert chemical names or chemical structures into the claim.

Claim Rejections - 35 USC § 103

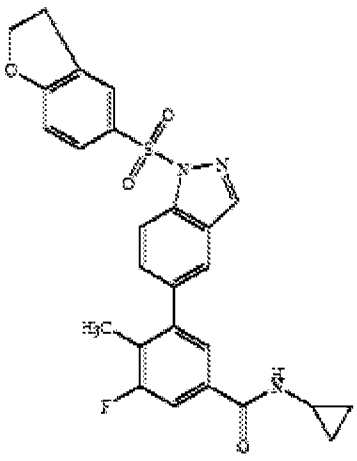
The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

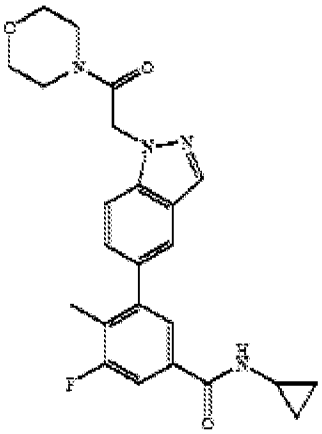
> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-11 and 15-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent Application No. US 2006/0122221 A1 by Angell et al. (NOTE: This reference was provided by Applicant in the Information Disclosure Statement filed 12/18/2008.) in view of International Application Publication No. WO 03/097610 A1 by Brill et al.

Determination of the scope and content of the prior art (MPEP §2141.01)

Angell et al. (see entire document; particularly pages 48-69) teach biaryl indazole compounds that are structurally similar to the instant claimed compounds. For instance, Angell et al. disclose the following compounds:





Example 111 **Example 138**

Ascertainment of the difference between the prior art and the claims (MPEP §2141.02)

The difference between the compounds of the prior art and the species instantly claimed is that the substituent on the indazole ring of instantly claimed species is a tetrahydro-*2H*-pyran ring with an intervening methylene group. Furthermore, Angell et al. suggest that the heterocycle off the indazole ring should only be a heterocycle containing nitrogen (page 71, lines 10-11).

Finding of prima facie obviousness--rational and motivation (MPEP §2142-2413)

Brill et al. disclose indazole compounds that also show activity as kinase inhibitors. Furthermore, Brill et al. demonstrate that the 3-position of the indazole ring may be substituted by a tetrahydrofuran ring containing moiety. (Page 47, Code C8) Therefore, a person having ordinary skill in the art at the time the invention was made would have recognized the potential use of oxygen-containing heterocycles on the same indazole core as disclosed by Angell et al. Furthermore, the same person having ordinary skill in the art at the time the invention was made would have been motivated to synthesize compounds based on the core structure of Angell et al. whereby the 1-position is substituted by an oxygen-containing heterocycle such as tetrahydro-2H-pyran or tetrahydrofuran with the hope of developing more compounds that demonstrate kinase inhibitory activity.

While the compounds reported by Brill et al. are position isomers of the compounds reported by Angell et al., the MPEP (2144.09) states “Compounds which are position isomers (compounds having the same radicals in physically different positions on the same nucleus) or homologs (compounds differing regularly by the successive addition of the same chemical group, e.g., by -

CH_2- groups) are generally of sufficiently close structural similarity that there is a presumed expectation that such compounds possess similar properties. In re Wilder, 563 F.2d 457, 195 USPQ 426 (CCPA 1977).

Double Patenting

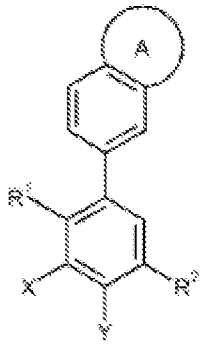
The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-11 and 15-18 are provisionally rejected on the ground of nonstatutory double patenting over claims 1-13 and 19-23 (from currently amended claims filed 4 April 2009) of copending Application No. 10/587790. This is a provisional double patenting rejection since the conflicting claims have not yet been patented.

The subject matter claimed in the instant application is fully disclosed in the referenced copending application and would be covered by any patent granted on that copending application since the referenced copending application and the instant application are claiming common subject matter, as follows: Application No. 10/587790 claims the following genus in claim 1:



where A is a fused 5-membered heteroaryl substituted by $-(CH_2)_m$aryl or $-(CH_2)_m$heteroaryl, R^1 is selected from methyl and chloro, R^2 is selected from $-NH-CO-R^6$ and $-CO-NH-(CH_2)_q-R^7$, X and Y are each independently selected from hydrogen, methyl and halogen. From the definitions enclosed in 10/587790 for the remaining R groups and alphabetic labels for chain length, the claims encompass the subject matter claimed in the present application.

Furthermore, there is no apparent reason why applicant would be prevented from presenting claims corresponding to those of the instant application in the other copending application. See *In re Schneller*, 397 F.2d 350, 158 USPQ 210 (CCPA 1968). See also MPEP § 804.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MATTHEW P. COUGHLIN whose telephone number is (571)270-1311. The examiner can normally be reached on Monday through Thursday from 7:30 am - 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, JAMES O. WILSON can be reached on 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Matthew P. Coughlin/
Examiner, Art Unit 4131

/James O. Wilson/
Supervisory Patent Examiner, Art Unit 1624